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**Abstract.** This paper presents an automated retinal vessel analysis system for the measurement and statistical analysis of vascular biomarkers. The proposed retinal vessel enhancement, segmentation, optic disc and fovea detection algorithms provide fundamental tools for extracting the vascular network within the predefined region of interest (ROI). Based on that, the artery/vein classification, vessel caliber, curvature and fractal dimension measurement tools are used to assess the quantitative vascular biomarkers: width, tortuosity, and fractal dimension. A statistical analysis on the extracted geometric biomarkers is set up using a dataset provided by the Maastricht study with the aim of exploring the associations between different vessel biomarkers and type 2 diabetes mellitus. A linear regression analysis is used to model the relationships between different factors. The results indicate that the vascular biomarker variables have associations with diabetes. These findings demonstrate the possibility of applying the proposed pipeline tools on further analysis of vessel biomarkers for the computer-aided diagnosis.

**Keywords:** Retinal image analysis · Vessel biomarkers · Computer-aided diagnosis · Diabetes mellitus

## 1 Introduction

The retinal fundus images provide a non-invasive way to ophthalmologists for investigating different eye-related and systemic diseases [2]. The major motivation of analyzing retinal blood vessels is that clinical findings demonstrate that physiological and pathological changes in the retinal vasculature are correlated with a variety of frequently occurring diseases [2,18]. Among them, diabetes mellitus is considered as one of the most epidemic diseases that cause blindness and


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vision loss, and hypertension is a leading effect of high mortality and morbidity worldwide. Other types of common systemic disorders caused by heart diseases or pulmonary diseases may also be observed in the geometrical changes of the retinal vascular network.

Automated detection of vascular changes in retinal images using digital image analysis methods has potentially huge benefits, as it offers the possibility of examining a large number of images, while saving labor time and costs, with more quantitative, reproducible and objective measurements than current manual observation techniques. Over the past years, a few automatic/semi-automatic systems have been developed mainly for research purpose [4,6,15] but the development of a fast and robust system is still an open task.

In *RetintaCheck* project,[1] a retinal image analysis infrastructure is set up for the automated detection and segmentation of important retinal landmarks, as well as for the assessment of vascular changes [5]. Subsequently, important vessel-based biomarkers are automatically computed from retinal images in a repeatable and objective manner. The algorithms used in this application outperform most of the state-of-the-art techniques [10]. In this paper, we investigate the correlation between the set of geometric biomarkers and the clinical metadata, and we show the most predictive and effective geometric biomarkers for early detection of diabetes.

## 2 Methodology

In previous works [5,7,10] of the *RetinaCheck* project, several retinal image analysis tools including automatic retinal vessel enhancement [1], segmentation [19–21], optic disc/fovea detection [8], artery/vein classification [10], caliber calculation [5], vessel curvature measurement [3] and fractal analysis [12,13] have been implemented to obtain important vessel biomarkers like central retinal arterial equivalent (CRAE), central retinal venous equivalent (CRVE), the arterial-venous diameter ratio (AVR), vessel tortuosity and fractal dimension. In Fig. 1, we illustrate how these modules interact with each other. Each of these modules and the computed biomarkers are explained in the following subsections. All of these tools and biomarkers assessment modules are integrated into one stand-alone application called retinal health information and notification system (RHINO) [7].

### 2.1 Vessel Enhancement and Segmentation

Retinal vascular analysis requires a well-extracted vessel tree from the original image. In the context of large-scale screening programs, we need an efficient and accurate vessel segmentation algorithm to assist ophthalmologists. Here we employ multi-scale rotating Gaussian derivative filters in orientation scores for the enhancement and segmentation of blood vessels [19,20]. The rotating derivatives are taken in the directions that are perpendicular to the vessel structures at

[1] http://www.retinacheck.org/.

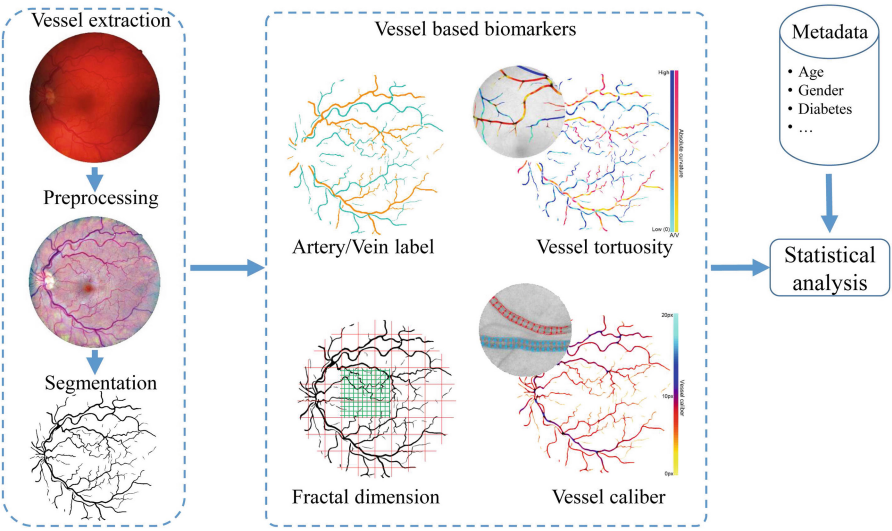


**Fig. 1.** The pipeline for the analysis of retinal vascular biomarkers.

their corresponding orientation planes. Disentangled vessel segments in the 3D orientation scores are enhanced by the rotating filters with proper scale samples, and afterwards the 2D enhanced vessel map is obtained by taking the maximum filter response over all orientations per position. By defining a proper threshold value on the enhanced image, the binary vascular map is finally obtained. This retinal vessel segmentation method has been validated on the public DRIVE [17] and STARE [11] datasets, where the segmentation results reach a sensitivity of 0.7473 and a specificity of 0.9764 for the DRIVE dataset, and 0.7676 and 0.9764 for the STARE dataset [20].

### 2.2 Optic Disc and Fovea Detection

In retinal image analysis, the optic disc (OD) and fovea locations are important landmarks to decide the protocolized region of interest (ROI) for the measurement of vascular geometry changes, such as the fractal dimension, tortuosity, CRAE, CRVE and central AVR. A predefined special ROI is able to provide consistent and reliable measurements in later biomarker analysis. In this paper, we rely on the automatic OD and fovea detection technique proposed by Dashtbozorg et al. [8], where a new convergence index operator, called super-elliptical filter (SEF) is presented. Furthermore, a setup for the simultaneous localization of the OD and fovea is introduced, in which the detection result of one landmark facilitates the detection of the other one. The paired SEF approach [8] has been evaluated on the MESSIDOR dataset [14] and achieves success rates of 99.75% and 98.87% for the OD and fovea detection, respectively. The region of interest

is defined as ring sector centered on OD center within 2 to 5 disc radius from the OD margin.

### 2.3 Artery/vein Classification

The retinal vasculature can be categorized into arteries and veins. The retinal arteries and veins behave differently under pathological conditions, and their geometrical changes are respectively considered as signs of several diseases. As such, it is important to define and study biomarkers separately for arteries and veins. A supervised approach [5] developed by the *RetinaCheck* group is used to classify the vessels into arteries and veins. In this method, we firstly obtain the vessel pixels from the vessel binary map. Then for each pixel, the artery/vein classification method extracts intensity-based features. After that, a logistic regression classifier and the set of selected features are used for the classification of arteries and veins.

## 3 Results

In this paper, linear regression analysis is used to find correlations between geometric biomarkers and diabetes status. The term "p-value" is used to refer to a probability that calculated after a given study. In statistical hypothesis testing, statistical significance (or a statistically significant result) is attained when a p-value is less than the significance level 0.05. The $\beta$ value (standardized regression coefficients) measures how severe each predictor variable modifies the criterion (dependent) variable and the sign (plus or minus) of the $\beta$ coefficient demonstrates the orientation of the relationship between variables.

### 3.1 Material

The Maastricht Study[2] is an observation study that focuses on Type 2 Diabetes Mellitus, comprising subjects that live in the southern part of the Netherlands and aiming to include 10,000 participants. This study takes a full examination of each subject, which lasts within a time window of 3 months, provides complete medical records including full blood, urine analysis, diabetic parameters: fasting glucose depletion rate, and fundus photography [16].

This paper analyzes a subset of the Maastricht Study data, consisting of the subjects of whom the retinal vasculature was photographed. The population consists of 1,943 subjects, including 971 males and 972 females, aged between 40 and 76, with an average of 59.8 years old and a standard deviation of 8.3. All the retinal images were acquired based on a non-mydriatic auto fundus camera (Model AFC-230, Nidek) in 45°. All the retinal images used in our study are OD centered ones and from the right eye of the subjects. The disease status in this subset is categorized into two groups: Healthy Individuals and Type 2 Diabetes Mellitus.

[2] https://www.demaastrichtstudie.nl/research.

### 3.2 Vessel Width

Vessel width is very important in the clinical study. The changes in vessel caliber directly reflect the change of blood flow viscosity and blood pressure in the vessels. In this paper, we measure the CRAE, CRVE and AVR of the retinal vasculature in a specific ROI. The full vessel caliber map is calculated based on the method in [19,20]. Once all arteries and veins are classified, the width-based biomarkers such as CRAE, CRVE and AVR are measured. An approach similar to the one described in [9] is applied for the estimation of the three biomarkers within predefined ROI.

The sign of $\beta$ (slope) and its corresponding p-value are calculated to see the associations between the vessel width based biomarkers and diabetes by considering age and gender factors are shown in Table 1. In this study, association between the CRVE and Type 2 Diabetes Mellitus is observed with a p-value of 0.027. The negative $\beta$ value means that an inverse correlation exists between them.

**Table 1.** The linear regression analysis of retinal vascular biomarkers with Type 2 Diabetes Mellitus (Maastricht study). A p-value below 0.05 is considered as a significant association and is marked in boldface. The sign of the $\beta$-value indicates a positive (+) or negative (−) association.

| Biomarkers | | Arteries (A) | | | Veins (V) | | | Both A/V | |
|---|---|---|---|---|---|---|---|---|---|
| | | sign($\beta$) | p-value | | sign($\beta$) | p-value | | sign($\beta$) | p-value |
| Vessel caliber | CRAE→ | + | 0.287 | CRVE→ | + | **0.027** | AVR→ | − | 0.747 |
| Vessel tortuosity | | + | 0.266 | | + | **0.040** | | + | 0.231 |
| Box dimension | | − | 0.261 | | + | 0.486 | | − | 0.527 |
| Lacunarity | | + | 0.315 | | + | 0.626 | | + | 0.260 |
| Box/Lacunarity raio | | − | 0.197 | | + | 0.788 | | − | 0.370 |

### 3.3 Vessel Tortuosity

For the assessment of biomarkers indicating the global tortuosity, the local curvature values are extracted from the curvature maps for the vessel pixels obtained. In this method an absolute curvature value is assigned to each pixel in the image. Afterwards, the average measurements of the entire distribution of curvature values from a single image are calculated within the defined ROI. The global tortuosity biomarkers are computed for different groups of vessels based on their types (artery and vein). Table 1 shows the correlations between the tortuosity and different diseases via linear regression analysis. The tortuosity values on veins present an association with the Type 2 Diabetes Mellitus with a p-value of 0.040.

### 3.4 Fractal Dimension and Lacunarity

In this paper, we estimate the fractal dimension of a vascular network by using the box dimension and the lacunarity [12,13]. The fractal dimensions are not

only computed on the full vascular network, but also on the arterial and venous network separately, using the result of artery/vein separation. As we can see in Table 1, the obtained statistical results give no significant correlation between the fractal dimension biomarkers and the Type 2 Diabetes Mellitus.

## 4 Conclusion

In this paper, we use a pipeline of analyzing vessel biomarkers to investigate the early detection of diabetes. A subset of clinical dataset from the Maastricht study is used to set up the statistical analysis of vessel biomarkers. Statistical analysis on the Maastricht study show the correlations between different vessel geometric biomarkers and diabetes. These statistics demonstrate that the proposed vessel analysis infrastructure based on our developed algorithms is useful to the computer-aided diagnosis, particularly for the large-scale screening programs. The validation phase is still ongoing and the application is currently being tested in Maastricht University Eye Hospital, on over 10,000 subjects and patients with a broad spectrum of clinical measurements.

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## References

1. Abbasi-Sureshjani, S., Smit-Ockeloen, I., Zhang, J., Romeny, B.T.H.: Biologically-inspired supervised vasculature segmentation in SLO retinal fundus images. In: ICIAR 2015. LNCS, pp. 325–334. Springer, Heidelberg (2015)
2. Abràmoff, M.D., Garvin, M.K., Sonka, M.: Retinal imaging and image analysis. IEEE Rev. Biomed. Eng. **3**, 169–208 (2010)
3. Bekkers, E., Zhang, J., Duits, R., Romeny, B.T.H.: Curvature based biomarkers for diabetic retinopathy via exponential curve fits in SE(2). In: Proceedings of the Ophthalmic Medical Image Analysis Second International Workshop, OMIA 2015 Held in Conjunction with MICCAI, pp. 113–120 (2015)
4. Cheung, C.Y.L., Zheng, Y., Hsu, W., Lee, M.L., Lau, Q.P., Mitchell, P., Wang, J.J., Klein, R., Wong, T.Y.: Retinal vascular tortuosity, blood pressure, and cardiovascular risk factors. Ophthalmology **118**(5), 812–818 (2011)
5. Dashtbozorg, B., Abbasi-Sureshjani, S., Zhang, J., Bekkers, E.J., Huang, F., ter Haar Romeny, B.M.: Infrastructure for retinal image analysis. In: Proceedings of the Ophthalmic Medical Image Analysis Second International Workshop, OMIA 2016, Held in Conjunction with MICCAI 2016, pp. 105–112 (2016)
6. Dashtbozorg, B., Mendonça, A.M., Penas, S., Campilho, A.: Retinacad, a system for the assessment of retinal vascular changes. In: 36th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, pp. 6328–6331. IEEE (2014)
7. Dashtbozorg, B., Zhang, J., Abbasi-Sureshjani, S., Huang, F., ter Haar Romeny, B.M.: Retinal health information and notification system (RHINO). In: Proceedings of SPIE Medical Imaging, vol. 10134, pp. 1013,437–1013,437–6. International Society for Optics and Photonics (2017)

8. Dashtbozorg, B., Zhang, J., Huang, F., ter Haar Romeny, B.M.: Automatic optic disc and fovea detection in retinal images using super-elliptical convergence index filters. In: Campilho, A., Karray, F. (eds.) Image Analysis and Recognition. Lecture Notes in Computer Science, vol. 9730, pp. 697–706. Springer (2016)
9. Dashtzbozorg, B., Mendonca, M.A., Penas, S., Campilho, A.: Computer-aided diagnosis system for the assessment of retinal vascular changes. In: Proceedings of the Ophthalmic Medical Image Analysis First International Workshop, OMIA 2014, Held in Conjunction with MICCAI 2014, pp. 9–16 (2014)
10. ter Haar Romeny, B.M., Bekkers, E.J., Zhang, J., Abbasi-Sureshjani, S., Huang, F., Duits, R., Dashtbozorg, B., Berendschot, T.T., Smit-Ockeloen, I., Eppenhof, K.A., et al.: Brain-inspired algorithms for retinal image analysis. Mach. Vis. Appl. **27**(8), 1117–1135 (2016)
11. Hoover, A., Kouznetsova, V., Goldbaum, M.: Locating blood vessels in retinal images by piecewise threshold probing of a matched filter response. IEEE Trans. Med. Imag. **19**(3), 203–210 (2000)
12. Huang, F., Dashtbozorg, B., Zhang, J., Bekkers, E., Abbasi-Sureshjani, S., Berendschot, T.T., ter Haar Romeny, B.M.: Reliability of using retinal vascular fractal dimension as a biomarker in the diabetic retinopathy detection. J. Ophthalmol. **2016**(6259047), 13 (2016)
13. Huang, F., Zhang, J., Bekkers, E., Dashtbozorg, B., ter Haar Romeny, B.: Stability analysis of fractal dimension in retinal vasculature. In: Proceedings of the Ophthalmic Medical Image Analysis Second International Workshop, OMIA 2015 Held in Conjunction with MICCAI 2015, pp. 1–8 (2015)
14. MESSIDOR, T.V.: Messidor: methods to evaluate segmentation and indexing techniques in the field of retinal ophthalmology (2014). http://messidor.crihan.fr/index-en.php. Accessed 9 Oct 2014
15. Ortega, M., Barreira, N., Novo, J., Penedo, M.G., Pose-Reino, A., Gómez-Ulla, F.: Sirius: a web-based system for retinal image analysis. Int. J. Med. Inform. **79**(10), 722–732 (2010)
16. Schram, M.T., Sep, S.J., van der Kallen, C.J., Dagnelie, P.C., Koster, A., Schaper, N., Henry, R.M., Stehouwer, C.D.: The Maastricht study: an extensive phenotyping study on determinants of type 2 diabetes, its complications and its comorbidities. Eur. J. Epidemiol. **29**(6), 439–451 (2014)
17. Staal, J., Abràmoff, M., Niemeijer, M., Viergever, M., Van Ginneken, B.: Ridge-based vessel segmentation in color images of the retina. IEEE Trans. Med. Imag. **23**(4), 501–509 (2004)
18. Wong, T.Y., Islam, F.A., Klein, R., Klein, B.E., Cotch, M.F., Castro, C., Sharrett, A.R., Shahar, E.: Retinal vascular caliber, cardiovascular risk factors, and inflammation: the multi-ethnic study of atherosclerosis (MESA). Invest. Ophthalmol. Vis. Sci. **47**(6), 2341–2350 (2006)
19. Zhang, J., Bekkers, E., Abbasi, S., Dashtbozorg, B., ter Haar Romeny, B.: Robust and fast vessel segmentation via Gaussian derivatives in orientation scores. In: Murino, V., Puppo, E. (eds.) Image Analysis and Processing. Lecture Notes in Computer Science, vol. 9279, pp. 537–547. Springer (2015)
20. Zhang, J., Dashtbozorg, B., Bekkers, E., Pluim, J.P.W., Duits, R., ter Haar Romeny, B.M.: Robust retinal vessel segmentation via locally adaptive derivative frames in orientation scores. IEEE Trans. Med. Imaging **35**(12), 2631–2644 (2016)
21. Zhang, J., Duits, R., Sanguinetti, G., ter Haar Romeny, B.M.: Numerical approaches for linear left-invariant diffusions on SE(2), their comparison to exact solutions, and their applications in retinal imaging. Numer. Math. Theor. Meth. Appl. **9**(1), 1–50 (2016)